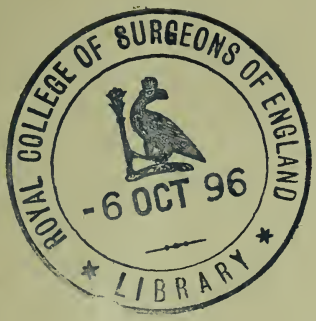
With the compliments of the author

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# DEGENERATIVE CHANGES IN THE BRAIN CELLS OF THE NON-INSANE.

By ROBERT HUTCHISON, M.B., M.R.C.P.Ed.

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# Degenerative Changes in the Brain Cells of the Non-Insane. By Robert Hutchison, M.B., M.R.C.P.Ed.

If the pathology of insanity is ever to be placed on a firm histological basis at all, one must first have some idea of the appearances presented by the cortical cells in a normal human brain. And by a "normal" I do not mean an ideal brain. Rather would I understand by it the average brain. The tendency in the past has been too much towards setting upon a pinnacle a nerve cell which corresponds to our notions of what a healthy nerve cell ought to be and making that the standard, all deviations from this being regarded as abnormalities. Our notions of what constitutes a healthy nerve cell have been derived from various sources, partly, perhaps, from the examination of the brains of the lower animals, partly from the appearances of the cortical cells of a few individuals who have been suddenly killed while in a state of perfect health. But this is setting up too high a standard. There are, after all, comparatively few organs which, when examined post mortem, come up to the type of health. The most casual listener in a post-mortem room must have been struck by the rarity with which a pathologist pronounces an organ to be healthy; and if this be so, it surely indicates that organs which exhibit considerable change after death may yet have shown no sign of disturbance of function during life. "The Compatibility of Normal Function with Abnormal Structure" would be an interesting chapter in general pathology. We seem to have been so constructed, that most, even of our most vital organs, work at comparatively low pressure, and are able to go on calmly performing their routine functions in a manner, at least not noticeably bad, even although the machinery is found, on close inspection, to be by no means as good as new.

And if this be so for the organs in general, why should the brain be an exception? We should, I venture to think, even on *a priori* grounds, expect many brains to show marked lesions after death, the owners of which exhibited no symptoms of mental impairment during life. Not so, however, the alienist. Deceived by the unduly high standard of health which has been set up, and almost entirely limited in his sphere of observations to the brains of the insane, he has been too apt to assume that any abnormal changes which he finds in the cortical cells after death must have had some causal connection with the mental state of the patient during life.

A wider outlook, however, might have whispered that there lurks here a fallacy. For a lunatic, after all, but rarely dies of his lunacy; usually he is carried off by an affection of his lungs, his kidneys, or his heart, just like his saner fellow creatures.

What right, then, has one to correlate a patient's mental symptoms with the changes found in his brain, until one has shown that these changes are not merely secondary, induced perhaps by disease in some other organ, but quite compatible with mental health, and occurring in all people who die of the same disease, whether insane or not? Obviously no right at all. Yet it will scarcely be denied that much of the so-called pathology of insanity rests upon such unstable foundations. How, then, are we to reach a proper point of view? How are we to correct our impressions of what a normal cortical cell is? There is only one way. We must examine a series of brains of persons dying from general diseases, and who have never suffered from insanity. We will thus get an idea of the appearance of the average cortical cell, and this average will serve as our standard of comparison. A brain which shows nerve cells deviating from the average in a marked degree, may then be regarded as abnormal. Such observations must be made on the brains of the sane by every method employed for the examination of the brains of the insane. And if we find that the insane show a larger proportion of brains which deviate from our normal standard than do the sane, then, and then only, are we

entitled to say that the disease insanity has, as its pathology, histological changes in the cortical nerve cells.

Such a normal standard the writer has endeavoured to establish for one method, the fresh method of Bevan Lewis. He has selected this method, not because it is necessarily the best now in existence for revealing the structure of the nerve cells, but chiefly because it is the method most in vogue with asylum pathologists, at least in this country; and also because of the fact that upon the results which it has afforded, much of the so-called pathology of insanity has been based. Let it be clearly understood that one's object was not to add to our knowledge of the minute structure of the normal human brain cell, but to arrive at some idea as to what sort of appearances may be expected to be found in a series of ordinary brain cells, apart altogether from the existence of insanity.

The method pursued was as follows:—The portion of brain examined, in each case, was a part of a convolution from the left motor area, the left ascending frontal convolution being that most usually selected. The portion of brain was frozen in the usual manner, fixed by immersion for 15–30 seconds in $\frac{1}{4}$ per cent. solution of osmic acid, stained for three quarters of an hour in $\frac{1}{4}$ per cent. analine blue-black, and mounted in balsam after drying. In all, 50 cases were examined. The naked-eye characters of the brain, the changes in the other organs, and the general nature of the illness from which the patient had died, were noted. No details of the patient's past history were, however, obtained, it being considered that if a sufficient number of cases were examined, ignorance of the history would not vitiate one's results.

What, then, did one find on examining these brains? The first thing with which one was struck was the frequency with which pathological changes occurred. It was, indeed, the exception, and not the rule, to find a brain which came up to one's preconceived notions of the state of health. I shall confine myself in this paper to the changes met with in the cells; vascular and other changes shall not be considered. I shall indicate also only the general nature and frequency of the changes met with. The pathological details of these changes are already so well known as to render any minute

description of them superfluous. In the accompanying plate, drawings are given taken from some of my preparations. These illustrate the general nature of some of the pathological appearances met with in a few of the cases examined.

Of all the lesions which were encountered, pigmentary degeneration was by far the most frequent. Now, it is extremely difficult to know when the amount of pigment in a cell oversteps the physiological limit. It is generally admitted that with increase of age an increase of pigment occurs. What, therefore, is normal for one time of life is by no means so for another. Even bearing this in mind, however, there was distinct evidence of an excess of pigment in nearly one-half of the abnormal specimens which I have met. In 59 per cent. of these the age of the individual was upwards of 45. In one of the most advanced, however, which I have seen, the age was only 38 years. All degrees of pigmentary degeneration were found, from a mere increase in the normal amount of pigment to a complete destruction of the cell, and its replacement by a mere heap of pigment granules.

The second stage of pigmentary degeneration described by Bevan Lewis, in which a condensation of the cell of the protoplasm occurs around the mass of pigment, I have not often been able clearly to identify. An excess of pigment was frequently to be observed in the vessel wall, and also in the pericellular and perivascular spaces, in those brains the cells of which showed pigmentary degeneration. The explanation of this frequent accumulation of pigment in the cells will be discussed later on; but, in the light of these observations, it is very difficult to accept the statement that it is "invariably a witness to bygone functional hyperactivity."

If it be difficult to say when pigment is in excess, even more difficult is it to be sure that the granularity of the cell protoplasm is more marked than normal. Certainly I have not often found typical examples of granular degeneration, at least not widespread throughout the cortex. In some cases I believe that I have been able to associate a granular change in the nerve cells, and loss of their processes, with the

occurrence of œdema throughout the entire brain, but to this I shall refer again later.

The vacuolation of the cells and of their nuclei is a change, the importance of which has been variously estimated. Originally described as characteristic of the brains of epileptics, it has been denied by others to be of any pathological significance at all. I think it is not unlikely that, in many cases, what has been described as vacuolated nuclei, are not really so at all. The nucleoli of the cortical cells stain very faintly with Bevan Lewis' method, and, in some instances, exactly simulate the appearance of holes in the nuclear body. It seems likely that these have, in many cases, been mistaken for true vacuoles. I think that this is the only conceivable explanation of such results as those published by Skae,[1] who asserts that he has found vacuolation of the nucleus in 80 per cent. of a series of brains which he examined from the insane. I have, however, found true vacuolation by no means infrequently, but, in many cases, affecting only one cell, or a small group of cells. The vacuoles have varied in size, from mere gaps in the nuclear substance to globular distension of the latter, sometimes causing complete disappearance of the nucleus, and invading the cell protoplasm. I have not been able to associate this change with any definite disease; and I cannot confirm the expectation of Campbell,[2] that these vacuoles will be found to be associated with toxæmic conditions. The appearances presented by some of the cells, in a case which I have recently examined, are illustrated in Plate XVIII.

Changes in the neuroglia do not appear to occur so frequently in the sane as they do in the insane. One meets not uncommonly with proliferation of cells around the vessels or immediately below the pia. Marked hypertrophy of spider cells I have not often encountered. In no case have I met with anything similar to what one finds in general paralysis.

I have indicated now the general nature of the results obtained, and, speaking roughly, one may say that they are the same in kind as those met with in insanity, with the

[1] Skae, *Brit. Med. Journ.*, London, May 19, 1894.

[2] Campbell, *Journ. Path. and Bacteriol.*, Edin. and London, vol. ii.

exception already mentioned of general paralysis of the insane. Are they, however, the same in degree? It could be plausibly argued that the insane brain differs from the non-insane only in so far that it exhibits the above changes with a greater frequency and a greater intensity. On this point the writer's absence of experience in mental disease hardly entitles him to speak with authority.

Through the kindness of Dr. Robertson, the present pathologist at the Morningside Asylum, an opportunity was afforded of comparing with the series of 50 non-insane brains another series of 50 derived from patients who had died in the asylum. These were taken in sequence without any selection, and had been prepared in precisely the same way as my own specimens. I am bound to say that I could find no greater intensity or frequency of the pathological change in the nerve cells in the one series than there was in the other, always excepting specimens from cases of general paralysis. Are we then to suppose that the majority of adults have, at the time of death, brain cells very far removed from the type which we have been accustomed to regard as normal? One would naturally hesitate to make such an affirmation until every other explanation had been exhausted. Some of these, which naturally suggest themselves, may be briefly dealt with.

And, in the first place, may the method itself not be at fault? May the freezing of the nerve cells, before they have been fixed, not lead to apparent structural alterations in their protoplasm, or may some other detail of the fresh method not be responsible for the frequency of change? That this may account for some appearances met with, it would be difficult indeed to deny. But that it will account for all, would be even more difficult to affirm. For why should the same method, carried out in precisely the same way, and by the same observer, yield, in one case, a section of a cortex which is a perfect picture, showing all the nerve cells and their processes in the greatest detail, and, in another case, exhibit nerve cells which are hardly recognisable as such at all. Further than this, nothing in the method could account for the occurrence of what is, after all, the commonest

change met with—the appearance in the cells of an excessive amount of pigment. The next possibility that presents itself is that the changes in the cells may really be of post-mortem production. In human pathology, of course, we cannot always make a necroscopy, even within twenty-four hours after death, and it is conceivable that the cells of the brain may undergo very rapid change, leading in some cases to partial disintegration. I have put this possible explanation to the test of experiment in the human brain. I have taken a brain and made sections from a convolution in the usual way. I have then laid the brain aside, taking care only to keep it cool and moist, and have then made other sections from the same convolution at later periods. I have allowed, in this way, one, two, three, and, in one case, even four days to elapse, and in comparing the late sections with the early I have been unable to find any difference at all between them. No appreciable change occurs even in four days. There is, of course, always a possibility that the post-mortem change occurs very rapidly within the first few hours after death, and, having reached a certain stage, then ceases. This hypothesis could only be tested on the brains of the lower animals, and I have not yet made any experiments in this direction.

It might again be contended that during a state of health the nerve cells are normal enough, but that in the last days of life the nutritive and other conditions of the brain are so altered, as, for example, they may be in a state of coma, that rapid degenerative changes set in. This explanation is thinkable, but I know not how it can be put to the test of experiment. In any case, we are not concerned with the validity of this, nor, indeed, of any of the above suppositions, for the brains of the insane are subjected to precisely the same post-mortem, and immediately ante-mortem conditions, as are those of the non-insane. Any explanation of the appearances presented in the one case, therefore, will apply with equal force to the other. Let us now turn to what is, after all, the most natural explanation that could be offered, that which would regard the changes in the cells as secondary to disease elsewhere. We have argued, in an earlier part of

this paper, that such secondary changes would be quite in harmony with the general teachings of pathology. Nay more; if there be any organ in which we should expect to meet such secondary changes, surely it is the brain. One has only to regard the richness of the blood supply to that organ to be convinced that it, beyond any other, must be profoundly affected, for good or for ill, by any changes in the circulatory system.

One meets with changes in other organs, due to chronic venous congestion, and why should not similar changes occur in the brain? Why, under such circumstances, should the liver cells show a deposit of pigment, and those of the brain not? And if a patient with such chronically congested liver does not show any signs of hepatic derangement, why should the other be expected to exhibit any symptom of insanity? But yet, on trying to correlate the changes I have found in the cerebral cells with disease of any particular viscus, I have met with no certain results. True, I have found, in some cases, pigmentary degeneration in the cerebral cells co-existing with obstruction to the venous return, *e.g.* in mitral stenosis, but, in other cases, such obstruction has been present in its typical form, without there being any accompanying change in the cerebral cells at all. The only disease, indeed, with which I have been able to correlate such changes in any degree at all, is chronic renal disease. I have examined the brains of six persons who died of that disorder, and in all of them degenerative changes were present in the cells. Especially did the cells of the deepest layers of the cortex seem to suffer. *A propos* of this, one recalls the fact that Bristowe has pointed out the analogy of the changes in the cerebral vessels in chronic Bright's disease with those that occur in general paralysis. It is also a well-known fact, worthy of particular mention in this connection, that chronic nephritis occurs with an abnormal degree of frequency among the insane. It is possible, however, that the changes in the cells are to be associated with the vascular disturbances in chronic nephritis, and not with the kidney lesion itself. It is only to be expected that a chronic state of œdema of the brain, even if only slight in degree, should lead to impairment

of nutrition in the cells, which may go on to actual degeneration. One's observations are not sufficiently numerous to justify a more dogmatic statement, but they indicate that the study of the minute changes which occur in the brain, as the result of disease in other organs, might lead to some interesting conclusions.

Regarding the results of this investigation as a whole, what is one to say? Are we to conclude that the pathology of insanity rests upon no histological basis at all? By no means. It must be remembered that only one method has been tested, and that not necessarily the best. If, however, it should prove, as it is not impossible that it may, that Nissl's and Golgi's methods also reveal the fact that the same changes occur in the brains both of the sane and the insane, then it would be necessary to prove that these changes are more frequent and more intense in the latter than in the former. Otherwise, there is but one hypothesis left, the rather nebulous hypothesis of "inherent instability of brain." That is to say, in an inherently stable brain the occurrence of slight degeneration in the nerve cells does not affect the working of the mental mill. Whereas if there be inherent instability, even a trivial change in the cells may upset the patient's mental balance. That, however, is an hypothesis which it is equally impossible either adequately to prove or satisfactorily to refute.

In closing, I must take the opportunity of recording my heartiest thanks to Drs. Muir and Leith, pathologists to the Royal Infirmary, for the facilities which they have invariably afforded me of obtaining the pathological material on which these observations are founded. To Dr. Ford Robertson also I feel myself deeply indebted, not only for the opportunity of examining a series of brains from the insane, but also for much friendly help and advice.

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## DESCRIPTION OF PLATE XVIII.

FIG. 1.—Early pigmentary degeneration. Female, æt. 35. Mitral stenosis. (× 450 diameters.) Note absence of staining in the nuclei.

FIG. 2.—Illustrates cells in a state of granular and of late pigmentary degeneration. The pigmentary cells are from the brain of a female, æt. 45, who died of chronic Bright's disease. The granular cells are from a man, æt. 43, who died of septicæmia, and in whom there was considerable œdema of the brain. (× 450 diameters.)

FIG. 3.—Vacuolation of nuclei and of cells, from male, æt. 54. Death from suppurative pancreatitis. (× 450 diameters.)

FIG. 4.—Colloid bodies below pia, from female, æt. 64; opium poisoning. (× 450 diameters.)

*Fig. 1.*

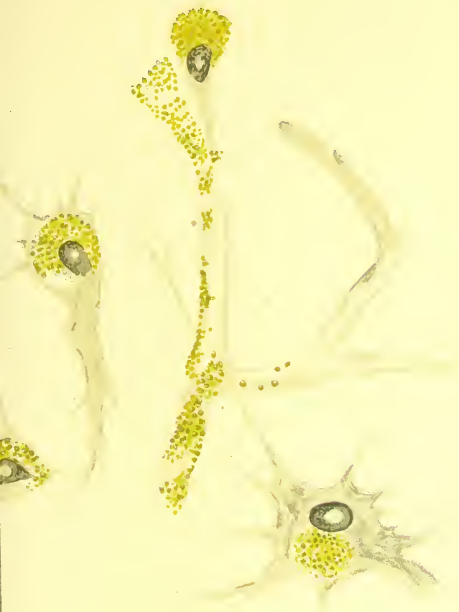

*Fig. 3*

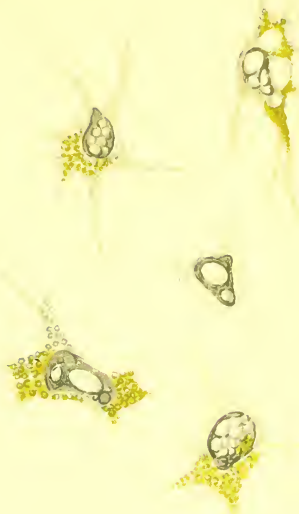

*Fig. 2.*

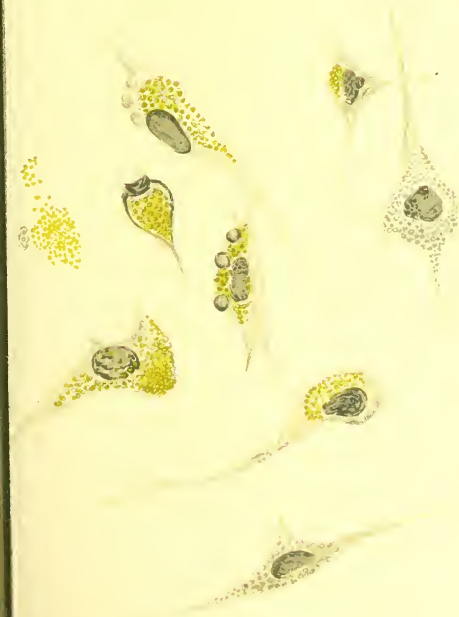

*Fig. 4.*